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Pharmaceutical Sciences **Review Article……!!!**

"A REVIEW ON MOLECULAR DOCKING AND SOFTWARE AVAILABLE FOR DOCKING STUDIES"

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KEYWORDS:

Docking, CADD, Protein Binding, Grid Generation, Ligand Preparation, Molecular Structure, Prediction Of Active Site, PDB (PROTEIN DATA BANK), Software Etc.

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ABSTRACT

Molecular docking is computational modeling of structure complexes formed by two or more interacting molecule. The goal of molecular docking is prediction of three-dimensional structure of interest. Molecular docking software mostly used in drug improvement. Molecules and effortless entrance to structural databases has essential mechanism. Molecular Docking provide a collection of expensive tools for drug design and analysis. The most important application of molecular docking is virtual screening. A variety of docking programs were residential to imagine the three-dimensional structure of the molecule and docking gain can also be analyze with the assist of dissimilar computational methods. Molecular docking is a key tool in structural molecular biology and computer-added drug design. Docking can be worn to execute virtual screening on large libraries of compounds, rank the results, and suggest structural hypotheses of how the ligands reduce the target, which is precious in lead optimization.

1. INTRODUCTION:

In the meadow of molecular modeling, docking is a technique which predict the prefer direction of one molecule to a second when jump to each other to form a steady compound [1]. Information of the chosen direction in rotate may be worn to expect the strength of involvement or binding affinity linking two molecules with each other.

The Suitable orientation of ligand molecule covers the receptor molecule to build a stable complex is called as molecular docking [1-3]. This orientation utilized for the binding affinity prediction and strength of connection of ligand and protein by using scoring function. The drug receptor interaction predicts the affinity and activity towards the molecule [4-5]. It plays vital role in drug design and drug discovery. It is minimized overall free energy of system. New drug discovery and development is very challenging task. With the help of In-Silico method new drug discovery occurs [8]. For the rapid gaining of drug discovery process the computer-based drug design should be used. It is useful in structural biology of molecule and computational drug design. It is used to anticipate the 3- D structure of molecule.

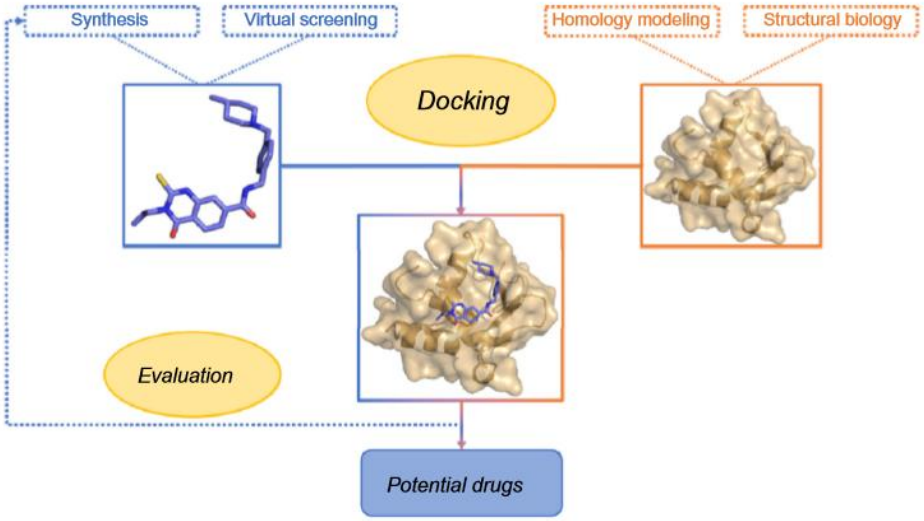

Fig [1]. Molecular docking by using potential drug.

COMPUTER AIDED DRUG DESIGN (CADD)

It is computer-based technique used in the computational chemistry to discover, enhance or study of drug and related biologically active molecule is called as (CADD) Computer Aided Drug Design.

1. It is most useful in new drug design.
2. It provides knowledge about the chemical and biological properties of ligands and targets.
3. It is used to find and improve novel drug.
4. Discovery of in-silico filters for prediction of undesirable properties like poor activity and poor Pharmacokinetic and Toxicity of drug molecule.

5. It is used for the optimization of novel drug targets.

6. By using chemical scaffolds to find out novel Virtual screening is applied for new drug molecules.

STRUCTURE-BASED DRUG DESIGN

Structure-based computer aided drug design depend on the knowledge of the target protein structure to calculate interaction energies for all tested compounds [43-46]. In structural database is crystallized target proteins are available. Structure- based is to design compounds that bind with minimal energy by specifically and tightly to the target [47-57].

A broader terminology, Virtual high-throughput screening, is a computer-based screening tool that allows screening of a large library of similar chemical compounds for a particular biological activity [58-65]. Virtual high-throughput screening comes in many forms, including: chemical similarity search, selecting compounds by predicted biologic activity through quantitative structure activity relationship (QSAR) models or pharmacophore mapping, and virtual docking of compounds against protein target of interest [66-74]. By using computational tools in the lead optimization phase of drug development is significant and cost benefit. Application of computational tools in hit-to-lead optimization while reducing the number of compounds that must be synthesized and tested In vitro.

TYPES OF MOLECULAR DOCKING

1 Search Algorithm: The experimentation method determines the binding modes and number of configurations creates. For docking analysis, the Monte Carlo method, fragment and genetic based, systemic searches is applied.

a. Rigid Docking

b. Flexible Docking

a. Rigid Docking: In this docking the receptor and ligand molecule both are fixed. Docking is performed. **b. Flexible Docking**: In this docking the ligand and the receptor both are movable. It is conformationally flexible. Each rotation the energy is calculated. Each conformation surface cell occupancy is calculated. After that the most optimum binding pose is selected.

2. Scoring Function: The binding affinity directly corresponding to the binding score. The best binders are best scoring ligands. It can be experimental, knowledge and molecular mechanics based. Docking Scoring is playing important role in designing of drug: a) Knowledge-based and b) Energy component methods DIFFERENT TYPES OF FORCES Bhagat et al.; JPRI, 33(30B): 46-58, 2021; Article no. 49 Fig. 3. Interactions different types

TYPES OF MOLECULAR DOCKING- The experimentation method determines the binding modes and number of configurations creates. For docking analysis, the Monte Carlo method,

fragment and genetic based, systemic searches is applied. In this docking the receptor and ligand molecule both are fixed. Docking is in this docking the ligand and the receptor both are movable. It is conformationally flexible. After that the most binding affinity is corresponding to the binding score. The best binders are best scoring ligands. It can be knowledge and molecular mechanics based. Docking Scoring is playing important role in designing of drug:

a) Knowledge-based scoring function the statistics of the observed inter contact frequencies in a large database of the crystal structure of protein complexes. Molecular interactions close to the maximum frequency of interactions in the data-base will have a high binding affinity. A molecular interaction with a low binding affinity in data base will have a low frequency of interaction.

b) Energy component scoring method based on the mathematical assumption that change in free energy upon binding of a ligand to a protein target (DG bind) is the sum of the free energy for ligand interaction, ligand-protein and solvent interaction, conformational changes in the ligand and protein and the motion in the ligand and protein target during complex formation [86-90].

MOLECULAR DOCKING MECHANICS STEPS -In In-Silico method studied the intermolecular interaction between 2 drug molecules. The protein receptor is Macromolecule. It acted as an inhibitor. The following steps involved in docking process are as follows.

Step I – **Preparation of protein and Ligand**: From Research Collaboratory Structural Bioinformatics Protein data bank (PDB) downloading the 3D-structure of the Protein. After that downloaded structure should be pre-processed. From removal of the water molecules, the charges stabilization, missing residues filling, add hydrogen atom side chains generation.

Step II –**Ligand Preparation-** By using different databases such as ZINC, Pub Chem Ligands molecule can be downloaded. It can be draw in Chem sketch tool in mol file. Then utilized LIPINSKY'S RULE OF 5 for this ligand molecule. It is used for the drug like and unlike molecules. It increases the high chance of success rate and decrease the failure Fig. 4. Fig. 6. Molecular docking mechanics steps TYPES OF MOLECULAR DOCKING Bhagat et al.; JPRI, 33(30B): 46-58, 2021; Article no. 50 Preparation of protein and Ligand: From Research Collaboratory Structural Bioinformatics Protein data bank (PDB) structure of the Protein. After that downloaded structure processed. From the cavity removal of the water molecules, the charges stabilization, missing residues filling, add hydrogen atom side chains by using different b Chem Ligands molecule can be downloaded. It can be draw in Chem sketch tool in mol file. Then utilized LIPINSKY'S RULE OF 5 for this ligand molecule. It is used for the drug like and unlike molecules. It increases the high chance of success rate and decrease the failure due to drug likeness properties for molecules.

Step III- **Grid Generation:** In this site, rotatable group, excluded volumes, constraints kept constant. The num operations performed (crossover, migration, mutation) is the key parameter in determining. Binding Cavity Prediction are to be done.

Step IV –**Prediction of Active site:** site of protein molecule should be predicted. After that Preparation of protein, the water molecules and hetero atoms if present they are removed from cavity.

Step V- **Docking:** Ligand and protein interactions are analyzed. Best docking score should be selected.

DRUG DESIGNING SOFTWARES

A computer needs software for its functions such as programs. This software makes our work simpler and faster. Various companies such as Accelrys, Schrodinger, Auto Dock and Argus Lab offering drug designing software's. (8)

1) Accelrys -Accelrys is a software company with its headquarters in US, along with its organization in Europe and Japan. It provides softwares especially for drug discovery and materials science. Their products and technologies create solutions for several stages in the drug discovery and developmental process4. The different software's produced by Accelrys are:

• Insight II
• Pipeline Pilot
• Discovery Studio
• Materials Studio
• Accord Insight II

Insight II is a graphical molecular modeling program. Using this software, we can build and manipulate virtually any class of molecules or molecular systems. Some of these insight II computational engines have the capacity to restart calculations from information's in the saved files.

2) Discovery Studio

Discovery studio is the advanced software solutions for life science researchers and is easy to use, a graphical interface for powerful drug design and protein modeling, sequence analysis, pharmacophore analysis and it is a structure-based designing software. Discovery studio provides a visualizing tool Active control, which provides 3D molecular structures and sharing scientific results. The sequence analysis is done by using tools such as BLAST (Basic Local Alignment

Search Tool) and protein modeling by DS Modeler. It can be operated in different operating system applications such as Linux and Windows based environment.

3) Pipeline

Pilot Pipeline Pilot data are based on powerful client server platform that leads to construct graphical workflows for data retrieval, filtering, and analysis.

4) Materials Studio

Materials studio software is the most advanced technology and is used to solve the problems in R&D process. It is designed for structural and computational researchers in chemicals and materials R&D. Material's studio provides tools for modeling crystal structure and crystallization processes; property prediction for molecules, polymers, catalysts and for determining the structure activity relationship. They provide various ranges of quantum mechanics-based tools for predicting structures, density functional methods, linear scaling and semi-empirical tools. QSAR integration in the Materials studio has wide range of descriptors such as topological and electro-topological descriptors, these helps the calculation process easier

5) Accord

Accord is software specially designed for cheminformatics. They can capture, manage, analyze, and my chemical data. Accord is oracle-based software used for storage, retrieval, analysis of chemical structures and related biological, chemical and inventory data. Accord is user friendly and is powered by Robust and well proven chemistry engine that can be used for any type of chemistry.

6) Schrodinger

Schrodinger software provides accurate, reliable and high-performance computational technology and provides facilities to solve problems in life science research. It was used for molecular modeling and well suited for drug designing both structures based and ligand-based methods. Most of the pharmaceutical companies, biotechnology companies, government agencies, universities and supercomputing centers are using this software. The various products of Schrodinger are:

1. Glide
2. Prime
3. Jaguar
4. Macro Model

Glide

Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level. Accurate binding mode prediction, Glide reliably finds the correct binding modes for a large set of test cases. It is good in terms of achieving lower RMS deviations from native co-crystallized structures. Glide offers a complete solution for ligand-receptor docking with speed and accuracy. Glide works with HTVS- High Through put Virtual Screening mode in which it can retrieve million compound libraries, to Standard Precise (SP) mode in which it docks hundreds to thousands of ligands with high accuracy. From SP it switches to XP Extra Precision where the false results are changed by advanced scoring. They can also exhibit excellent range of docking accuracy across diverse range of receptors. This makes the glide universally applicable.

Prime

Prime is a package used for protein structure predictions. It is user friendly. Prime provides users complete control over calculational settings to increase the accuracy of the result, they provide accurate receptor models for structure-based drug design. Homology modeling and fold recognition can be done using prime. Comparative modeling is used to generate accurate homology models for further structure-based studies. Threading and fold recognition techniques are used in cases of low or no sequence identity. Prime allows the users to specify and adjust parameters to optimize the quality of predictions.

Jaguar

Jaguar is a high-performance ab-into package for both gas and solution phase recreation, with particular strength in treating metal containing systems. Jaguar proceeds faster than the other conventional methods and it makes more possible to carry out more calculations at a single time. Jaguar computes a comprehensive array of molecular properties such as NMR, IR, pKa, partial charges, electron density, electrostatic potential and NBO analysis. It also generates potential energy surface with respect to differences in the internal coordinates.

Macro Model

Macro Model is a complete molecular modeling packaging suitable using leading force fields which provides accurate results. Forcefield molecular modeling is used to examine molecular conformations, molecular motions and inter molecular interactions such as ligand receptor complex. It can also perform molecular dynamics at constant temperatures using mixed Monte Carlo algorithm and stochastic dynamics. They help wide range of searching methods and handling systems in the range of small molecules to entire proteins. Different types of force

fields such as MM2, MM3, AMBER, AMBER 94, MMFF, and OPLS-AA are supported by Macro Model to do a wide range of research applications.

Auto Dock

Auto Dock is a pack of automated docking tools which is designed to dock small molecules, like how substrates or drug candidate binds to the receptor of a known 3D structure. It consists of two programs: 1. Auto Dock – it performs docking of the ligand with the target molecule which is a protein.

2. Auto Grid pre calculates this binding of the ligand with the target molecule. This type of study can help in designing better binders. Auto Dock Tools (ADT) has been developed to set up which type of bonds is rotatable in the ligand to analyze the docking.

Auto Dock has several applications in-

1. X-ray crystallography
2. Structure based drug design
3. Lead Optimization
4. Virtual Screening (HTS)
5. Combinational library design
6. Protein-Protein docking
7. Chemical mechanism studies.

Flex X

Flex X is another fragment-based method using flexible ligands and rigid proteins. It uses MIMUMBA torsion angle database for the creation of conformers. The MIMUMBA is an interaction geometry database used to exactly describe intermolecular interaction patterns. For scoring, the Boehm function (with minor adoptions necessary for docking) is applied. Flex X is introduced here to pronounce the importance of scoring functions. On the contrary to DOCK which performs well with a polar binding site, Flex X shows totally opposite behavior. It has a bit lower hit rate than DOCK but provides better estimates of Root Mean Square Distance for compounds with correctly predicted binding mode. There is an extension of Flex X called Flex E with flexible receptors, which has shown to produce better results with significantly lower running times.

GOLD

GOLD uses genetic algorithm to provide docking of flexible ligand and a protein with flexible hydroxyl groups. Otherwise, the protein is considered to be rigid. This makes it a good choice when the binding pocket contains amino acids that form hydrogen bonds with the ligand. GOLD uses a scoring function that is based on favorable conformations found in Cambridge Structural

Database and on empirical results on weak chemical interactions. GOLD has one of the most comprehensive validation test sets and is also available for use at CSC. Shows good results in impartial tests. It has a good hit rate overall; however, it somewhat suffers when dealing with hydrophobic binding pockets.

Argus lab

Argus lab is molecular modeling software that runs on windows. It is free software and can be easily accessed by the public. It consists of a user interface that displays the graphical structure of the molecules and runs quantum mechanics calculation using Argus Computing Server. By using Argus lab, we can able to build an atom, build molecules using templates, to change the structure of an atom and bond types, and to build new structures from the preexisting structures.

Ligand binding is the key step in enzymatic reactions for their inhibition. Therefore, a detailed understanding of interactions between small molecules and proteins may form the basis for a rational drug design strategy another example, which is emphasized here, is the successful use of docking to design lead compounds as new anti-infectious agents against Mycobacterium tuberculosis or Plasmodium falciparum. These two pathogens are the key actors in the development of tuberculosis and malaria, respectively, which are the two major causes of mortality in developing countries. In order to target this scourge, several research teams have studied, for a long time now, the no mevalonate isoprenoid biosynthesis pathway (2-methyl- d-erythritol-4-phosphate [MEP] pathway). Indeed, these parasites rely on this cascade to produce their own isoprenoid compounds, critical for their survival. The second step of the pathway is the reduction of 1-deoxy-d-xylulose-5- phosphate to MEP catalyzed by 1-deoxy-d-xylulose-5-phosphate reductoisomerase (DXR). In addition, humans and animals do not rely on the MEP pathway, making DXR an attractive target in the search for novel families of drugs. Currently, several inhibitors of DXR have been synthesized and evaluated.

The purpose of this subsection is to present the usage of structural data in order to improve the efficiency of a new family of drugs. In the absence of crystallographic structures of DXR from P. falciparum (pf-DXR) or M. tuberculosis, molecular modeling, based on the structure of DXR from Escherichia coli, allowed several research groups to further elucidate the structure and function of the enzyme and also facilitated structure-based inhibitor design. Consequently, models of DXR from the pathogens were built and used to develop efficient screening methods in order to identify potential lead compounds. Later, these models were validated by X-ray crystallography. [6]

Solvent effect as an important parameter

Proteins in solution are surrounded by water molecules. Water molecules around proteins organize in hydration shells that show correlated fluctuations. They are responsible for electrostatic screening and make important contributions to enzyme substrate recognition and catalysis and to molecular recognition in general. Considerable effort has been devoted to the modeling of water molecules in protein–ligand docking procedures, where the importance of water-mediated contacts has long been recognized. Well-known docking packages such as GOLD AUTODOCK, or GLIDE can incorporate water molecules explicitly to predict protein–ligand docking poses. But very few methods exist that allow the prediction of hydration water positions at protein–protein interfaces. The important contribution of water in the binding between proteins is readily realized when considering the high-affinity complex. The extracellular ribonuclease is always expressed with its inhibitor in order to prevent the bacterium from degrading its own RNA. The complex has been extensively studied both experimentally and computationally, explaining in detail its binding energetics. [9]

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